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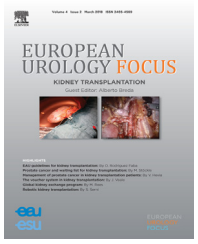

Prostate Cancer

Safety and Antitumour Activity of ODM-201 (BAY-1841788) in Chemotherapy-naïve and CYP17 Inhibitor-naïve Patients: Follow-up from the ARADES and ARAFOR Trials

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Abstract

Background: ODM-201, a new androgen receptor antagonist for treatment of metastatic castration-resistant prostate cancer (mCRPC), demonstrated antitumour activity and acceptable tolerability in phase 1/2 trials.
Objective: To determine the antitumour activity and safety profile of extended treatment with ODM-201 in men with mCRPC.
Design, setting, and participants: ARADES and ARAFOR trials with ODM-201 enrolled chemotherapy-naïve and CYP17 inhibitor (CYP17i)-naïve mCRPC patients. Both trials had extended follow-up. Here we report results for chemotherapy-naïve and CYP17i-naïve patients from both trials (data cutoff October 2014 for ARADES and April 2015 for ARAFOR) after extended follow-up.
Intervention: A total of 41 chemotherapy-naïve and CYP17i-naïve patients received oral ODM-201 twice daily (total daily dose of 1200, 1400 or 1800 mg).
Outcome measurements and statistical analysis: Antitumour activity was assessed in terms of prostate-specific antigen (PSA) declines and PSA/radiographic progression. Safety was assessed until disease progression and/or drug discontinuation due to any intolerable adverse event (AE).
Results and limitations: ODM-201 safety data after a median treatment time of 13.5 mo (95% confidence interval [CI] 9.7–15.6, interquartile range [IQR] 7.5–22.0) were similar to those reported in the main ARADES and ARAFOR trials. The overall AE incidence was 80.5% (n = 33/41), with 58.5% (n = 24/41) of patients experiencing only grade 1–2 AEs. The most common AEs were fatigue, back pain, diarrhoea, nausea, and pain in extremity. The median times to PSA and radiological progression were 12.4 mo (95% CI 6.3–18.2, IQR 5.5–22.0) and 15.3 mo (95% CI 9.5–not reached [NR], IQR 6.3–NR), respectively.
Conclusions: Extended treatment with ODM-201 (1200–1800 mg/d) was well tolerated, with no new safety concerns, and provided evidence of sustained antitumour activity in chemotherapy-naïve and CYP17i-naïve patients with mCRPC.
Patient summary: Prolonged treatment with high doses of ODM-201 was well tolerated and provided long-lasting disease control in patients with mCRPC. ODM-201 represents a therapeutic treatment option for mCRPC.
The ARAFOR trial (including the follow-up stage) and the follow-up component of the ARADES trial are registered with ClinicalTrials.gov as trial numbers NCT01784757 and NCT01429064.

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1. Introduction

Prostate cancer (PCa) is the third most common cause of cancer-related death in men in the EU, with an estimated 92 000 deaths in 2012 [1]. Androgen deprivation therapy (ADT), via either orchiectomy or treatment with a luteinising hormone–releasing hormone agonist/antagonist, is the standard of care for patients with hormone-sensitive advanced PCa [2,3]. Despite an initial response to treatment, most patients progress to metastatic castration-resistant PCa (mCRPC), which has a poor prognosis [2,4,5] and requires subsequent therapeutic intervention [6,7].

Alterations in the androgen receptor (AR) signalling pathway are the main underlying molecular mechanism driving mCRPC [8–10]. As tumour growth of PCa cells in the castration-resistant disease stage is dependent on persistent AR signalling, the AR axis is considered an effective therapeutic target in mCRPC [11,12]. Specific androgen axis- and AR-targeting agents—abiraterone and enzalutamide—have been approved in the EU and the USA for mCRPC treatment. Both compounds improved overall survival and radiographic progression-free survival and had a beneficial impact on quality of life (QoL) in phase 3 trials including post-chemotherapy [13–15] and pre-chemotherapy [16,17] mCRPC patients. New AR inhibitors are being developed for treatment of mCRPC, including ODM-201, an investigational nonsteroidal oral AR antagonist that is structurally different from any other antiandrogen compound, including enzalutamide and apalutamide [18]. A preclinical study showed that ODM-201 has antitumour activity in vivo, as it inhibited tumour growth in a murine VCap CRPC xenograft model, with higher activity than enzalutamide [18].

In two phase 1/2 trials, ODM-201 exhibited antitumour activity and was well tolerated in men with mCRPC. In the open-label multicentre ARADES trial (NCT01429064), a non-randomised, first-in-man, dose escalation phase 1 ($n = 24$) showed that antitumour activity was achieved at all doses tested (200–1800 mg/d) and no dose-limiting toxicity was observed [19]. In the phase 2 extension ($n = 110$), a prostate-specific antigen (PSA) decline was observed with all ODM-201 doses tested (200–1400 mg/d), and the 1400-mg/d dose led to the greatest PSA response in chemotherapy-naïve and CYP17 inhibitor (CYP17i)-naïve patients. Furthermore, ODM-201 was well tolerated, with >99% of adverse events (AEs) being grade 1–2 [19].

ARAFOR (NCT01784757) was an open-label multicentre trial that included a pharmacokinetic component ($n = 30$) and an open-label extension study ($n = 30$) [20]. ODM-201 demonstrated antitumour activity and was well tolerated in chemotherapy-naïve patients: a PSA response (≥50% decrease in PSA levels from baseline at week 12) was observed in 25/30 patients (83%), and 91% of treatment-emergent AEs were of grade 1–2 [20].

With the previous findings from the ARADES and ARAFOR trials, the safety and tumour-suppression activity of extended ODM-201 dosing in men with mCRPC are of clinical interest, as these patients usually benefit from prolonged treatment. Here we report data from the follow-up of the ARADES and ARAFOR trials on the safety and antitumour activity of ODM-201 in patients with mCRPC, who did not receive prior chemotherapy or CYP17i.

2. Patients and methods

2.1. Study design and patients

The data presented here from the ARADES (cutoff date October 31, 2014) [19] and ARAFOR (cutoff date April 30, 2015) trials [20] include those patients who were chemotherapy- and CYP17i-naïve and received 1200, 1400 or 1800 mg/d of ODM-201. The complete study design was published previously [19,20]. In brief, male patients were aged ≥18 yr, had progressive mCRPC, an Eastern Cooperative Oncology Group performance status (ECOG-PS) score of 0–1, and serum testosterone levels <1.7 nmol/l. Patients were included if they were mildly symptomatic or asymptomatic and those with a history or risk of seizures could be included. Patients without bilateral orchidectomy had to continue approved ADT during the trial.

In the ARADES and ARAFOR trials, disease progression was defined by: rising PSA (two consecutive increases in PSA levels ≥1 wk apart, with the lowest value being ≥2 ng/ml); radiographic disease progression (assessed using the modified Response Evaluation Criteria in Solid Tumours version 1.1); or the presence of two or more new bone lesions. Exclusion criteria were the presence of brain metastases and prior treatment with AR antagonists, CYP17i or chemotherapy.

2.2. Ethics

Patients gave written informed consent and the trials were approved by an independent ethics committee at each centre or by the investigational review board. The trials were conducted according to the principles of the Declaration of Helsinki and the guidelines for Good Clinical Practice.

2.3. Treatment

Patients received ODM-201 twice daily with food (total daily dose of 1200, 1400 or 1800 mg). Treatment continued until disease progression or an intolerable AE.

2.4. Antitumour activity assessments

In the ARADES and ARAFOR trials, PSA concentrations were measured at baseline, every 4 wk until the 9-mo visit, every 3 mo thereafter, and at the end-of-study visit. The percentage change in serum PSA was calculated from baseline until patients discontinued the study. Baseline PSA was defined as the PSA level before the first ODM-201 dose.

The median time to PSA progression was defined as the time from ODM-201 treatment initiation until documentation of a ≥25% increase and an absolute increase of ≥2 ng/ml in PSA from nadir, according to Prostate Cancer Working Group 2 criteria [21]; this had to be confirmed by an additional PSA measurement ≥3 wk later. A minimum period of 12 wk was required before PSA progression could be declared. Time to radiographic progression was defined as the time between the start of treatment and the occurrence of the first progression (soft tissue or bone) as assessed using computed tomography/magnetic resonance imaging or a bone scan.

2.5. Safety and tolerability

AEs were classified by system organ classes and preferred terms (Medical Dictionary for Regulatory Activities coding system, version 17.1 in the ARADES trial, and 18.0 in the ARAFOR trial) and graded by the National

Cancer Institute of Common Terminology Criteria for AEs (version 4.03). Laboratory assessments (haematology, serum biochemistry, hormones and urine analysis) were performed: at baseline, once a week for the first 28 d, every 4 wk until the 9-mo visit, every 3 mo thereafter, and at the end-of-study visit. Hormone measurements were performed up to week 12.

2.6. Statistical analysis

Antitumour activity and safety analyses included all patients who received at least one dose of ODM-201. Time to PSA and radiographic progression were calculated using Kaplan-Meier estimates; the median values with associated 95% confidence intervals (CIs) and interquartile ranges (IQRs) are reported. All measurements are summarised using descriptive statistics. Analyses were performed using data collected up to the cutoff dates of October 31, 2014 for ARADES and April 30, 2015 for ARAFOR.

3. Results

3.1. Patients

A total of 41 patients with progressive mCRPC were included in the analyses; they were all chemotherapy-naïve and CYP17i-naïve. Of these, 30 (73.2%) were from the ARAFOR trial and 11 (26.8%) from the ARADES trial.

Baseline demographic and clinical characteristics of the patients were well balanced in the two trials (Table 1). The median age was 69.0 yr (range 54.0–86.0) and most patients (73.2%) were classified as ECOG-PS score 0. The overall baseline median PSA was 27.7 ng/ml (range 3.5–1293.8); most patients had bone disease at screening (n = 36, 87.8%), whereas 16 patients (39.0%) had disease localised in the lymph nodes and three patients (7.3%) had visceral disease.

Data for patients from the ARADES trial were collected until October 31, 2014; the initial results were reported in 2014 using a cutoff date of October 3, 2013 [19]. Patient data from the ARAFOR trial were collected through to April 30, 2015 and the initial results were published in 2015 with a cutoff date of October 31, 2014 [20]. The difference in cutoff dates between the two studies presented here reflects the different study initiation dates [19,20].

All patients from the ARAFOR trial (30/41, 73.2%) received 1200 mg/d of ODM-201, while ARADES patients received 1400 mg/d (n = 9/41, 22.0%) or 1800 mg/d (n = 2, 4.9%). Overall, 30/41 patients (73.2%) discontinued the study; the most common cause of discontinuation was

Table 1 – Baseline demographics and clinical characteristics.

	ARADES trial (n = 11)	ARAFOR trial (n = 30)	Total (n = 41)
Age (yr)	73.0 (62.0–82.0)	68.0 (54.0–86.0)	69.0 (54.0–86.0)
PSA (ng/ml)	219.2 (14.9–1293.8) [a]	18.2 (3.5–554.8)	27.7 (3.5–1293.8) [b]
Testosterone (ng/dl)	0.7 (0.4–1.7)	0.8 (0.4–1.6)	0.8 (0.4–1.7)
LDH (U/l)	193.0 (159.6–515.0) [a]	323.5 (163.0–559.0)	287.0 (159.6–559.0) [b]
Gleason score at diagnosis			
2–6	1 (9.1)	6 (20.0)	7 (17.1)
7	4 (36.4)	12 (40.0)	16 (39.0)
8–10	5 (45.5)	12 (40.0)	17 (41.5)
Missing [c]	1 (9.1)	0 (0.0)	1 (2.4)
ECOG-PS			
0	10 (90.9)	20 (66.7)	30 (73.2)
1	1 (9.1)	10 (33.3)	11 (26.8)
Time from diagnosis to SS (mo)	64.1 (10.9–165.7)	39.7 (7.6–133.7)	50.0 (7.6–165.7)
Prior antiandrogen therapy	11 (100.0)	22 (73.3)	33 (80.5)
LHRH therapy	10 (90.9)	30 (100.0)	40 (97.6)
Time from LHRH therapy to SS (mo)	40.7 (6.6–153.3) [d]	22.5 (0.9–126.6) [e]	22.5 (0.9–153.3) [f]
Disease localisation			
Lymph node	4 (36.4)	12 (40.0)	16 (39.0)
Bone disease	9 (81.8)	27 (90.0)	36 (87.8)
Bone only	7 (63.6)	15 (50.0)	22 (53.7)
Bone and soft tissue	2 (18.2)	12 (40.0)	14 (34.1)
Soft tissue only	2 (18.2)	3 (10.0)	5 (12.2)
Visceral	1 (9.1)	2 (6.7)	3 (7.3)
Bone metastases at screening			
0	2 (18.2)	3 (10.0)	5 (12.2)
1–4	3 (27.3)	9 (30.0)	12 (29.3)
5–20	3 (27.3)	4 (13.3)	7 (17.1)
>20 or non-countable	3 (27.3)	14 (46.7)	17 (41.5)

ECOG-PS = Eastern Cooperative Oncology Group performance status; LDH = lactate dehydrogenase; LHRH = luteinising hormone-releasing hormone; PSA = prostate-specific antigen; SS = study start.
Data are presented as median (range) for continuous variables and as n (%) for categorical variables.
[a] n = 10.
[b] n = 40.
[c] Gleason score not available.
[d] n = 8.
[e] n = 29.
[f] n = 37.

disease progression (90% of patients), with only two patients (6.7%) discontinuing due to AEs and one (3.3%) for personal reasons. Four ARADES patients whose treatment was ongoing after the original data cutoff of October 3, 2013 [19] discontinued the extension study before the new cutoff date of October 31, 2014. Of the ten patients who were ongoing by October 31, 2014 in the main ARAFOR trial [20], one discontinued the extension follow-up before the new cutoff date of April 30, 2015 and one discontinued study treatment, but not the study, before the extended data cutoff.

Although the median follow-up time was 15.3 mo (95% CI 10.4–16.5, IQR 7.9–25.7; Fig. 1) and the median on-treatment time was 13.5 mo (95% CI 9.7–15.6, IQR 7.5–22.0), 11 patients (n = 10 ARAFOR and n = 1 ARADES) continued the study after the data cutoff. Of these, ten patients (n = 9 ARAFOR and n = 1 ARADES) continued ODM-201 treatment after the data cutoff: two patients were on a named patient (compassionate) use basis, with one patient receiving treatment until the end of August 2016, for a total on-treatment time of 41 mo.

3.2. Safety

An AE was experienced by 80.5% (n = 33/41) of patients, and 29 patients (70.7%) had more than one AE. The most common AEs of any grade were: fatigue (grade 1) in eight patients (19.5%); nausea (grade 1–3), pain in extremity (grade 1–2), back pain (grade 2–3) and diarrhoea (grade 1–2) in five patients (12.2%); and arthralgia (grade 1–2) in four patients (9.8%) (Table 2). Overall, 24 patients (58.5%) had only grade 1–2 AEs and seven patients (17.1%) experienced grade 3 AEs, including: PCa progression, back pain, nausea, bone pain, increase in blood alkaline phosphatase, hypertension, hyponatraemia, lung adenocarcinoma, fall and femoral neck fracture (Table 2). Grade ≥4 AEs were observed only in the ARAFOR trial and included respiratory failure and neuroendocrine carcinoma (two patients), and one patient died due to general physical health deterioration and PCa progression (Table 2). The pattern of AEs reported during this study in chemotherapy-naïve and CYP17i-naïve patients is similar to that reported in the same patient population during the main ARADES and ARAFOR trials: at the time of the original cutoff dates (October 3, 2013 for ARADES and October 31, 2014 for ARAFOR), the most common AEs of any grade included grade 1 fatigue/asthenia (8 patients, 19.5%); diarrhoea and pain in extremity (grade 1–2) and grade 1–3 nausea (5 patients, 12.2%); and grade 2–3 back pain and grade 1–2 peripheral oedema (4 patients, 9.8%). Furthermore, during the main ARADES and ARAFOR trials the incidence of grade 3 AEs (4 patients, 9.8%) was similar to that reported during the follow-up (7 patients, 17.1%); overall, no new AEs (any grade) were observed in the follow-up.

During this study, treatment-related AEs occurred in ten patients (24.4%): four patients (36.4%) were from the ARADES trial and six (20.0%) from ARAFOR (Table 3). All treatment-related AEs were grade 1; the most common were fatigue (3 patients, 7.3%) and hot flush (2 patients, 4.9%).

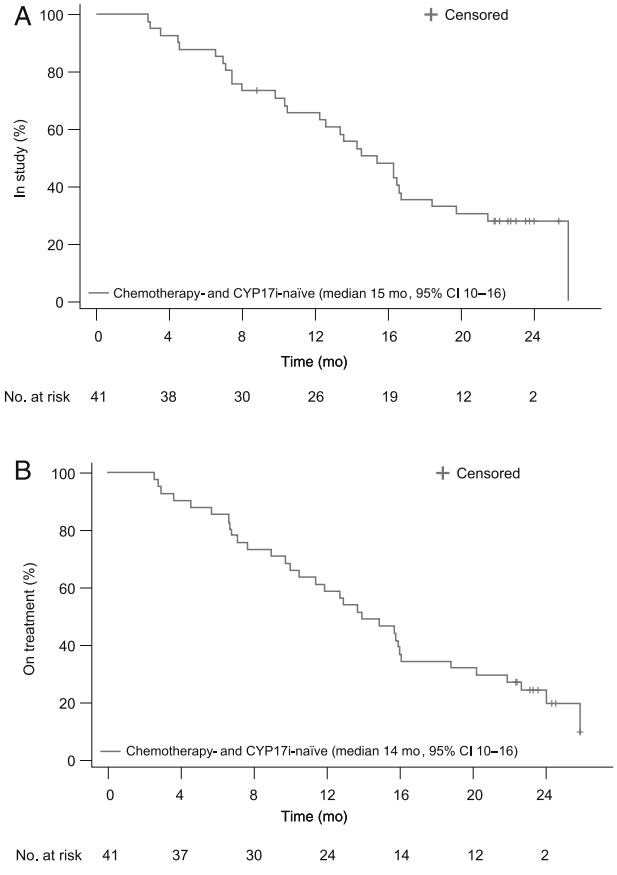

Fig. 1 – Kaplan-Meier estimate of (A) follow-up and (B) time on treatment. CI = confidence interval.

3.3. Antitumour activity

The percentage PSA change from baseline for each patient during treatment with 1200, 1400, and 1800 mg/d of ODM-201 is shown in Fig. 2A. The maximum PSA response rate (≥50% PSA reduction from baseline at any time during the study) was 85% (n = 34/40); this was 80% (n = 8/10) and 87% (n = 26/30) in the ARADES and ARAFOR trials, respectively (Fig. 2B).

The median time to PSA progression was 12.4 mo (95% CI 6.3–18.2, IQR 5.5–22.0) for all patients (Fig. 2C). This was slightly longer in the ARAFOR trial (12.5 mo, 95% CI 5.4–not reached [NR], IQR 4.6–NR) than in the ARADES trial (9.9 mo, 95% CI 5.5–22.0, IQR 7.6–19.6). Similar data were obtained for the time to radiological progression; this was 15.3 mo (95% CI 9.5–NR, IQR 6.3–NR) in the ARAFOR trial, but was not reached in the ARADES trial (95% CI 2.6–NR, IQR 14.0–NR).

4. Discussion

Analysis of the extended follow-up of patients from the ARADES and ARAFOR trials indicated that for up to 25.7 mo (median 15.3), treatment with high doses of ODM-201 (1200, 1400 and 1800 mg/d) was well tolerated and provided durable antitumour activity in chemotherapy-naïve and CYP17i-naïve patients with mCRPC. These results are consistent with the findings reported for the earlier stages

Table 2 – Adverse events (AEs).

	Patients reporting AEs, *n* (%)			
	Grade 1–2	Grade 3	Grade 4	Grade 5
Any AEs				
ARADES (*n* = 11)	11 (100.0)	1 (9.1)	0 (0.0)	0 (0.0)
ARAFOR (*n* = 30)	21 (70.0)	6 (20.0)	2 (6.7)	1 (3.3)
Total (*n* = 41)	32 (78.0)	7 (17.1)	2 (4.9)	1 (2.4)

	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Grades 1–5
Common AEs [a] (*n* = 41)						
Fatigue	8 (19.5)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	8 (19.5)
Nausea	4 (9.8)	1 (2.4)	1 (2.4)	0 (0.0)	0 (0.0)	5 (12.2)
Pain in extremity	5 (12.2)	1 (2.4)	0 (0.0)	0 (0.0)	0 (0.0)	5 (12.2)
Back pain	0 (0.0)	4 (9.8)	1 (2.4)	0 (0.0)	0 (0.0)	5 (12.2)
Diarrhoea	4 (9.8)	1 (2.4)	0 (0.0)	0 (0.0)	0 (0.0)	5 (12.2)
Arthralgia	2 (4.9)	2 (4.9)	0 (0.0)	0 (0.0)	0 (0.0)	4 (9.8)
Bone pain	1 (2.4)	2 (4.9)	1 (2.4)	0 (0.0)	0 (0.0)	3 (7.3)
Haematuria	3 (7.3)	1 (2.4)	0 (0.0)	0 (0.0)	0 (0.0)	3 (7.3)
Influenza	2 (4.9)	2 (4.9)	0 (0.0)	0 (0.0)	0 (0.0)	3 (7.3)
Abdominal pain	2 (4.9)	1 (2.4)	0 (0.0)	0 (0.0)	0 (0.0)	3 (7.3)
Dysuria	3 (7.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	3 (7.3)
Headache	3 (7.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	3 (7.3)
Hot flush	3 (7.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	3 (7.3)
Hypertension	0 (0.0)	2 (4.9)	1 (2.4)	0 (0.0)	0 (0.0)	3 (7.3)
Rash	2 (4.9)	1 (2.4)	0 (0.0)	0 (0.0)	0 (0.0)	3 (7.3)
Rhinorrhoea	3 (7.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	3 (7.3)
Vomiting	2 (4.9)	1 (2.4)	0 (0.0)	0 (0.0)	0 (0.0)	3 (7.3)
Prostate cancer	0 (0.0)	1 (2.4)	1 (2.4)	0 (0.0)	1 (2.4)	3 (7.3)

[a] AEs occurring in ≥5% of patients.

of the two trials [19,20]: in the ARADES trial, patients without prior chemotherapy and CYP17i treatment who received 1400 mg/d of ODM-201 were those who showed the greatest PSA suppression [19]. ODM-201 dose levels used in this study were based on the efficacy observed in the main ARADES [19] and ARAFOR [20] trials in patients receiving higher doses of study medication, and are consistent with the study design of two planned phase 3 ODM-201 trials, ARAMIS (NCT02200614) and ARASENS (NCT02799602), in which patients will receive the 1200 mg daily dose of ODM-201.

Table 3 – Treatment-related adverse events (TRAEs) [a].

	Patients reporting grade 1 TRAEs, *n* (%)
Any TRAE	
ARADES (*n* = 11)	4 (36.4)
ARAFOR (*n* = 30)	6 (20.0)
Total (*n* = 41)	10 (24.4)
All TRAEs (*n* = 41)	
Fatigue	3 (7.3)
Hot flush	2 (4.9)
Abdominal pain	1 (2.4)
Constipation	1 (2.4)
Decreased appetite	1 (2.4)
Diarrhoea	1 (2.4)
Dizziness	1 (2.4)
Dysgeusia	1 (2.4)
Flatulence	1 (2.4)
Gynaecomastia	1 (2.4)
Headache	1 (2.4)
Nasopharyngitis	1 (2.4)
Nausea	1 (2.4)
Poor peripheral circulation	1 (2.4)
Solar dermatitis	1 (2.4)
Somnolence	1 (2.4)
Tinnitus	1 (2.4)
Urinary incontinence	1 (2.4)

[a] All TRAEs were of grade 1.

The ODM-201 safety profile after extended use is consistent with data previously reported for the ARADES and ARAFOR trials [19,20] and no additional safety concerns were observed. Most patients analysed here (*n* = 32/41, 78.0%) experienced AEs of grade 1–2; likewise, in the main ARAFOR and ARADES trials, most AEs (116/129, 90%, and 82/83, 99%, respectively) were of grade 1–2 among all the AEs reported. Of these, the most common events were fatigue (grade 1 in 8/41, 19.5%) and nausea (grade 1–3 in 5/41, 12.2%), which are clinically relevant AEs in mCRPC and are commonly observed during treatment with AR antagonists [13,16,22–25]. The incidence of AEs in chemotherapy-naïve and CYP17i-naïve patients analysed here is similar to that reported in the same patient population during the main ARADES and ARAFOR trials at the time of the original cutoff dates, demonstrating that extended ODM-201 treatment is not associated with any new safety concerns.

On the basis of these data, the safety of ODM-201 compares favourably with that reported for other AR antagonists, such as enzalutamide, whose long-term safety profile was established in chemotherapy-naïve patients in a phase 1/2 trial [23] from which patients with a known risk of seizure were excluded. For both AR antagonists, the most commonly reported treatment-emergent AEs following extended treatment were fatigue and nausea, observed in 19.5% (grade 1 fatigue) and 12.2% (grade 1–3 nausea) of

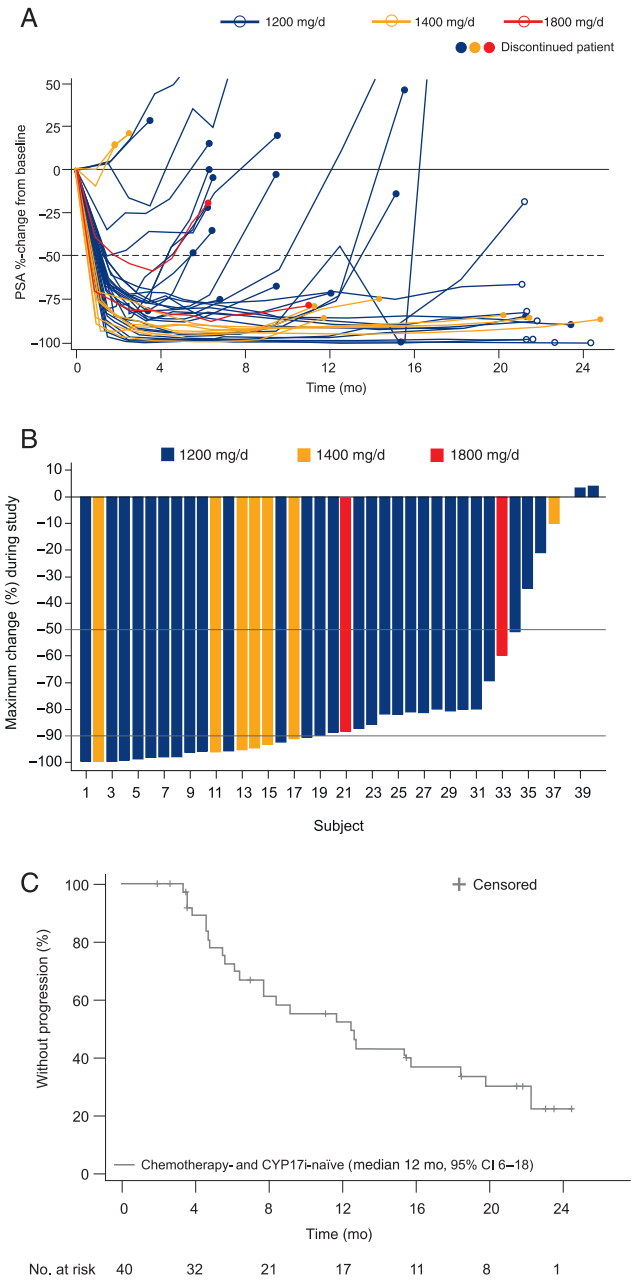

Fig. 2 – (A) Prostate-specific antigen (PSA) percentage change from baseline, by subject, truncated at +50%. (B) Maximum PSA percentage change from baseline during study, by subject. (C) Time to PSA progression. CI = confidence interval.

patients treated with ODM-201; in enzalutamide-treated men, fatigue occurred in 72% (any grade) of patients, with 15% experiencing grade 3/4, whereas nausea (any grade) was reported by 31% of patients [23]. The incidence of fatigue during extended ODM-201 treatment reported here is also lower than that seen in phase 3 trials of enzalutamide (36% all grades and 2% grade ≥3) [16] and abiraterone acetate (39% all grades and 2% grade ≥3) [17] in patients who had not received chemotherapy. Importantly, no seizures were reported after extended treatment with ODM-201. This may be explained by the lower likelihood of ODM-201 crossing the blood-brain barrier, as shown in preclinical studies, and may be related to the unique chemical structure of ODM-201; additional trials are needed to confirm these findings [18,26]. Prior enzalutamide trials reported treatment-related seizures [13,23,24], and preclinical studies suggested that enzalutamide may cross the blood-brain barrier and bind to GABA receptors [13,24,27,28], thereby increasing the risk of seizures.

In addition to a favourable tolerability profile, prolonged treatment with ODM-201 provided sustained antitumour activity: a decrease in PSA levels from baseline was maintained over time in most chemotherapy-naïve and CYP17i-naïve patients at all doses tested (Fig. 2A,B), similar to the ARADES and ARAFOR trials. The median times to PSA progression (12.4 mo, 95% CI 6.3–18.2) and radiological progression (15.3 mo, 95% CI 9.5–NR) were similar to data from the main ARAFOR trial (12.4 mo, 95% CI 5.3–NR; and 15.2 mo, 95% CI 9.4–18.2) but were shorter than those reported for chemotherapy-naïve and CYP17i-naïve patients from the ARADES main trial (16.6 mo, 95% CI 5.6–NR; and NR, 95% CI 8.4–NR).

A limitation of this analysis is that, being a non-randomised phase 1/2 trial, there was no control group and a relatively small number of patients was included ($n = 41$). Therefore, although multiple doses were tested, no definitive conclusion may be drawn regarding the optimal efficacy of each ODM-201 dose. Nevertheless, the promising antitumour activity and favourable safety profile of ODM-201 provide a basis for future confirmatory phase 3 trials [29]. In this regard, the efficacy and safety of ODM-201 are currently being evaluated in large placebo-controlled phase 3 trials among men with high-risk nonmetastatic CRPC (ARAMIS, NCT02200614) and men with metastatic castration-sensitive prostate cancer (ARASENS, NCT02799602). Another limitation is that QoL measurements were not included during this follow-up analysis. As a spectrum of neurocognitive psychological effects have been associated with ADT and AR inhibitors, further studies are warranted to assess the effect of extended ODM-201 treatment on patient-reported QoL [30].

5. Conclusions

Extended treatment with ODM-201 at doses of 1200–1800 mg/d continued to show encouraging antitumour activity in patients with mCRPC who had not received prior chemotherapy and CYP17i. No additional or unexpected safety signals were observed beyond those reported at the initial analysis points of the ARADES and ARAFOR trials. ODM-201 may represent a well-tolerated and effective treatment option for patients with mCRPC.

Author contributions: Neal D. Shore had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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Acquisition of data: Shore, Tammela, Massard, Bono, Fizazi.
Analysis and interpretation of data: Shore, Tammela, Massard, Bono, Aspegren, Mustonen, Fizazi.
Drafting of the manuscript: Shore, Fizazi, Mustonen.

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